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Trabecular bone score and bone turnover markers in men with DISH: Data from the Camargo Cohort study

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ABSTRACT

Objective: Diffuse idiopathic skeletal hyperostosis (DISH) has been associated with an increased risk of vertebral fracture. To date, no studies have investigated the relationship between DISH and bone microstructure assessed by the trabecular bone score (TBS).
Methods: Cross-sectional study, nested in a prospective population-based cohort. All men (968) aged≥50 years were included. Clinical covariates, DISH, TBS, serum bone turnover markers and bone mineral density (BMD) were analyzed.
Results: Mean age of participants was 65 ± 9 years. 207 (21.6%) had DISH. DISH subjects were older, had higher body mass index (BMI) and abdominal perimeter, lower glomerular filtration rate (GFR), and higher prevalence of metabolic syndrome (MetS) than non-DISH (NDISH) subjects. Bone mineral density at the lumbar spine (LS-BMD) was significantly higher in the DISH group. TBS values were 1.317 [1.303–1.331] for DISH and 1.334 [1.327–1.341] for NDISH subjects, after adjusting by age, BMI, abdominal perimeter, arterial hypertension, diabetes mellitus, MetS, GFR, serum alkaline phosphatase (ALP), LS and femoral neck BMD (p = 0.03). Serum ALP levels were higher in DISH subjects, showing an inverse correlation with TBS that remained significant after adjusting by age and BMI.
Conclusions: TBS values were significantly lower in men with DISH irrespective of age, BMI and BMD, suggesting that the presence of DISH might be related to a worse trabecular microstructure.

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a non-inflammatory rheumatic disorder characterized by ossification of ligaments, tendons and joint capsules, first described by Forestier and Rotés-Querol in 1950 [1,2]. It can affect numerous locations, but the involvement of the anterior vertebral ligament of the thoracic spine is the most characteristic manifestation of the disease [3,4]. DISH is more frequent in older men and its pathogenesis remains unknown, although genetic, mechanical and metabolic factors, mainly abdominal obesity, have been involved [4,5]. Furthermore, growth factors, bone morphogenetic proteins (BMP) or adipokines, have also been implicated in DISH pathogenesis, since they would act on the fibroblasts, chondrocytes and collagen fibers of the entheses promoting bone neoformation [6].

DISH is usually an asymptomatic condition, although joint pain, limited axial mobility, dysphagia, airway obstruction, as well as increased susceptibility to vertebral fractures, have been reported [7–9]. These fractures are often associated with neurological complications and higher mortality rate [10]. The role of bone mineral density (BMD) in the development of vertebral fractures in subjects with DISH represents a matter of debate [11]. High BMD values have been reported in these patients, both in the axial [12] and in the appendicular skeleton [13–15], which would paradoxically imply a lower risk of fracture. In fact, it has been pointed out that the bone in DISH is denser but at the same time more fragile [7]. However, some other authors have questioned this observation, suggesting that high BMD values measured by dual-energy x-ray absorptiometry (DXA) may be overestimated, due to the effect of anterior vertebral ligament ossification [11].

Nevertheless, there are other factors that can contribute to the risk of fracture, independently of BMD, such as the rate of bone turnover, the degree of matrix mineralization, the geometry (dimensions, cortical thickness) or the integrity of the trabecular structure, all

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dynamic processes that, together with BMD, determine bone strength [16,17].

Data on bone biomarkers in patients with DISH are scarce, and increased levels of osteocalcin, secreted frizzled-related proteins and sclerostin and decreased levels of dickkopf-related protein 1 (DKK-1) have been reported [18,19].

Trabecular bone score (TBS) is an image technique developed to indirectly evaluate the state of the trabecular microarchitecture based on the information provided by the standard DXA [20]. It consists of a texture parameter that evaluates pixel gray-level variations in the projected lumbar spine DXA image. Thus, TBS may be considered as an overall index of bone quality and low values have been associated with a worse bone structure and a higher risk of fracture [20,21]. The usefulness of TBS in fracture risk assessment or for therapeutic recommendations in patients with osteoporosis has been addressed in a recent Position Development Conference by The International Society for Clinical Densitometry [22].

To our knowledge, TBS values in patients with DISH have not been reported to date.

Based on these considerations, our aim has been to assess the TBS values in a population-based cohort of men aged 50 years or older, with and without DISH. Given the paucity of data, a second objective has been to compare the serum levels of markers of bone formation and bone resorption in DISH and non-DISH (NDISH) subjects.

Patients and methods

Population and sample

The study population included all the men aged ≥50 years taking part in a prospective population-based cohort, the Camargo Cohort, whose full details have been previously published [23]. Briefly, the Camargo Cohort was set up in 2006 to assess the prevalence and incidence of bone metabolic diseases in postmenopausal women and men aged ≥50 years, who attended two health care centers in Cantabria, Spain.

At baseline, patients were asked to complete a questionnaire on bone metabolism and general diseases, current or past medication use and risk factors for osteoporosis and fragility fractures. Moreover, blood samples were collected and all the participants underwent lateral thoracic and lumbar spine radiographs and a DXA exam. The Camargo Cohort study was approved by the Clinical Research Ethics Committee of Cantabria (Internal Code 2014.155). All participants gave written informed consent.

Participants whose baseline assessment revealed the presence of diseases or treatments known to affect bone metabolism, such as osteoporosis, primary hyperparathyroidism, hyperthyroidism, serum creatinine >1.7 mg/dl (151 μmol/L), or use of bisphosphonates, estrogen, raloxifene, strontium ranelate, teriparatide, L-thyroxin, anticonvulsants or glucocorticoids in the previous year, were excluded. We also excluded patients with previous diagnosis of ankylosing spondylitis or chronic liver disease.

Clinical variables

Weight (in kg), height (in meters) and abdominal perimeter (in cm) were obtained with the subjects wearing underwear and without shoes. Body mass index (BMI) was measured in kg/m^2, considering obesity when BMI ≥ 30 kg/m^2. Physical activity was categorized as sedentary (sitting in a chair most of the time, short walks outside the house), light (shopping, domestic work) or moderate-intense (daily -or most days- exercise or intense work).

Smoking was defined as non-smokers or smokers (current smokers and ex-smokers). Alcohol intake was defined as a daily consumption greater than 20 g [24].

Blood samples were obtained from an antecubital vein in the morning after a requested 12-hour overnight fast. Serum concentrations of calcium, phosphorus, albumin and total alkaline phosphatase (ALP) were obtained by automated methods in an ADVIA® 2400 Chemistry System autoanalyzer (Siemens, Germany). Serum concentrations of 25-hydroxyvitamin D (25-OHD), intact parathyroid hormone (iPTH), amino-terminal pro-peptide of type 1 collagen (PINP) and C-terminal telopeptide of type 1 collagen (CTX) were determined by an automated method of electrochemiluminescence (Elecsys® 2010, Roche Diagnostics, GmbH, Mannheim, Germany). The detection limits for iPTH, P1NP and CTX were 6 pg/ml, 5 ng/ml and 0.01 ng/ml, and the normality ranges were 15–65 pg/ml, 15–78 ng/ml and 0.069–0.760 ng/ml, respectively. The glomerular filtration rate (GFR) was estimated according to the CKD-EPI formula [25] and expressed in ml/min/1.73 m^2. Metabolic syndrome (MetS) was defined according to the NCEP-ATPIII criteria [26].

BMD was measured by DXA, with a Hologic® QDR-4500 device, at the lumbar spine (LS-BMD), femoral neck (FN-BMD) and total hip (TH-BMD). In-vivo precision was 0.4–1.5% at different locations, and the results were expressed in gr/cm^2. All measurements were made by the same operator. The measurement of the TBS has been carried out from the images of the DXA in LS (L1-L4) stored in the densitometer memory, with the TBS iNsight software (TBS iNsight® v2.1, Medimaps, Mérignac, France) installed in the densitometer.

Two independent trained researchers, blinded to clinical data, evaluated DISH and vertebral fractures. DISH was diagnosed according to the Resnick and Niwayama criteria [27]: ossifications affecting the anterior longitudinal vertebral ligament of at least 4 contiguous vertebral bodies, a relative preservation of the intervertebral disk space in the affected segment without signs of degenerative disk changes, and the absence of apophyseal joint degeneration or sacroiliac inflammatory changes. The grade of vertebral fracture was assessed by the semiquantitative method of Genant [28].

Statistical analysis

Quantitative variables were expressed as mean±standard deviation (SD) or median [interquartile range], and categorical variables, in percentage. Student-*t*-test, Mann-Whitney U test, median test and ANOVA, were used to compare quantitative variables, and Pearson's chi-squared test in the case of categorical variables. The relationships between variables were initially analyzed through bivariate correlations using Pearson or Spearman coefficients and then, univariable linear regression models. The risk was expressed as prevalence odds ratio (OR) with 95% confidence interval (95% CI). A general linear regression model was built to assess the relationship between DISH and TBS, including the covariates that showed significant differences between DISH and NDISH groups. Bonferroni adjustment for multiple testing was also carried out. A p-value <0.05 was considered statistically significant in all the analyses.

Results

A total of 1113 men aged ≥50 years were initially recruited. Of them, 145 were excluded because of incomplete data or having diseases or receiving treatments that affect bone metabolism. Thus, 968 participants (mean age, 65 ± 9 years; range, 50–92 years) were finally included in the study, and 207 of them (21.6%) were diagnosed with DISH.

DISH was associated with age (r = 0.202; p<0.0001) and BMI (r = 0.111; p = 0.001). Thus, increasing prevalence of DISH was observed in the elderly (15.6% in subjects <65 years vs. 29.2% in those ≥65 years; p < 0.0001) and in obese participants (17.3% in subjects with BMI <30 vs. 28.8% in those with BMI ≥30; p<0.0001).

The main epidemiological characteristics of participants with and without DISH are summarized in Table 1. DISH subjects were older,

Table 1
Baseline clinical characteristics according to DISH status.

	DISH (*N* = 207)	NDISH (*N* = 761)	*P*
Age, *yrs.*	67 (15)	62 (13)	0.0001
Body mass index, *Kg/m²*	29.9 (4.4)	28.7 (4.1)	0.0001
Abdominal perimeter, *cm*	105 (12.7)	101 (12)	0.0001
Obesity, *n (%)*	103 (49.7)	257 (33.7)	0.0001
Diabetes mellitus, *n (%)*	46 (22.2)	142 (18.6)	0.27
Arterial hypertension, *n (%)*	118 (57)	356 (46.8)	0.01
Dyslipidemia; *n (%)*	75 (36.2)	260 (34.1)	0.58
GFR, *ml/min/1.73 m²*	74.4 (21.8)	78 (23)	0.01
Metabolic syndrome; *n (%)*	99 (47.8)	238 (31.2)	0.0001

NDISH: Non-DISH. GFR: glomerular filtration rate.
Quantitative variables are expressed in median (interquartile range).

had higher BMI and abdominal perimeter, lower GFR, and higher prevalence of MetS than NDISH participants had. Besides, LS-BMD was significantly higher in DISH subjects compared to the NDISH group (Table 2), also with increased values in the oldest men: 1.044 vs. 0.988 g/cm^2 in the group <65 years (p = 0.002), and 1.073 vs. 0.986 g/cm^2 in those ≥65 years (p = 0.006).

TBS was inversely correlated to age (r = −0.179; p<0.0001) and BMI (r = −0.467; p<0.0001). TBS median values were 1.328 [1.222−1.405] in the DISH group vs. 1.352 [1.255−1.433] in NDISH subjects (p = 0.02) (Table 2). The presence of DISH was associated with a lower TBS: 57.1% of the DISH subjects had a TBS below the median of the whole sample (1.346), compared to 48.7% of the NDISH subjects, with an unadjusted OR value of 1.40 (95% CI 1.03−1.92); p = 0.03. After adjusting by age, BMI, abdominal perimeter, arterial hypertension, diabetes mellitus, MetS, GFR, ALP, LS-BMD and FN-BMD, TBS values were 1.317 [1.303−1.331] and 1.334 [1.327−1.341] in DISH and NDISH groups, respectively (p = 0.03).

As the TBS shows better performance when BMI ranges from 15 to 35 kg/m^2 [29], this issue was addressed by previously excluding subjects with BMI >35 kg/m^2 in the analysis. However, the results did not virtually change when including these subjects (adjusted TBS value of 1.325 [1.314−1.336] in DISH vs 1.339 [1.331−1.347] in NDISH participants; p = 0.02)

Regarding bone biomarkers, subjects with DISH had higher serum ALP levels than NDISH individuals (p = 0.049), while PINP and CTX levels were similar in both groups. Serum ALP levels showed an inverse correlation with TBS (r = −0.104; p = 0.001) that remained significant after adjusting by age and BMI. No correlation was observed between TBS values and serum PINP or CTX levels.

Table 2
Bone metabolism parameters according to DISH status.

	DISH (*N* = 207)	NDISH (*N* = 761)	*P*
Trabecular bone score (TBS), *unitless*	1.328 (0.2)	1.352 (0.1)	0.02
Vertebral Fracture; *n (%)*	43 (20.7)	151 (19.8)	0.76
History of fracture> 40 years old; *n (%)*	31 (15)	122 (16)	0.71
Albumin, *g/dl*	4.4 (0.3)	4.5 (0.5)	0.60
Calcium, *mg/dl*	9.5 (0.5)	9.5 (0.6)	0.65
Phosphate, *mg/dl*	3 (0.5)	3 (0.7)	0.39
iPTH, *pg/ml*	51.5 (24.6)	51.8 (24)	0.37
25(OH)D, *ng/ml*	22 (10.8)	22 (11)	0.42
Alkaline phosphatase, *U/L*	67 (23)	64 (22)	0.049
P1NP, *ng/ml*	35.5 (20.5)	34 (18.7)	0.32
CTX, *ng/ml*	0.2 (0.2)	0.2 (0.2)	0.50
LS BMD, *g/cm²*	1.05 (0.2)	0.98 (0.2)	0.0001
FN BMD, *g/cm²*	0.82 (0.2)	0.80 (0.1)	0.04
TH BMD, *g/cm²*	0.98 (0.1)	0.97 (0.1)	0.11

NDISH: Non-DISH. 25(OH)D: 25-hydroxyvitamin D; iPTH: intact parathyroid hormone; P1NP: amino-terminal pro-peptide of type 1 collagen; CTX: C-terminal telopeptide of type 1 collagen. BMD: bone mineral density; LS; lumbar spine; FN: femoral neck; TH: total hip.
Quantitative variables are expressed in median (interquartile range), with the exception of total hip BMD, expressed as mean (standard deviation).

Discussion

To our knowledge, this is the first study that assesses the TBS values in DISH subjects. We have shown that there is an inverse relationship between DISH and TBS, independently of age, BMI, BMD, and other covariates. This finding might represent a biologically plausible explanation, among others, of the propensity to vertebral fractures independently of BMD found in patients with DISH.

Despite the great variability, the observed prevalence of DISH of 21.6% in men >50 years is in line with the data reported in studies based on plain radiographs [30]. The clinical characteristics of DISH patients observed in our study were also similar to those previously published, specifically the higher average age and the higher prevalence of obesity [5]. Likewise, age has also been inversely associated with TBS values [20], as observed in our study. Besides, obesity was significantly more prevalent in our DISH group, and BMI and TBS were inversely correlated. In this sense, there is a well-known relationship between obesity and DISH [4,5]. Serum adipokines with effect on the regulation of bone metabolism (mainly leptin and adiponectin) have been suggested as a potential pathophysiological link [31−33]. Furthermore, the metabolic environment of obesity (insulin resistance and inflammation) may be associated with impaired bone health in obese individuals [34]. With regard to TBS values in obese subjects, a recent report has found that obesity was associated with a low TBS in men, irrespective of BMD [35].

Concerning bone biomarkers in patients with DISH, there is not yet a clearly established pattern. We have evaluated two serum markers of bone formation, ALP and PINP, and a marker of bone resorption, CTX. ALP values were significantly higher in the DISH group and have shown an inverse correlation with TBS. In the same line, increased ALP levels have been reported in DISH subjects [36]. Moreover, experimental studies seem to support this clinical observation, since an increase in ALP activity has been observed in ligament cells cultures from patients with DISH, reflecting the transformation of these cells into osteoblasts [37]. Some studies have reported that the changes of the total ALP with age are essentially due to the bone isoenzymes, and in fact, elevated ALP in postmenopausal women has been reported to be mainly caused by high bone turnover [38]. Serum osteocalcin has also been reported to be increased in patients with DISH [18,39]. The higher levels of ALP and the inverse correlation with TBS in DISH subjects might reflect the sensitivity of trabecular bone to an increased bone turnover [40]. Nevertheless, serum PINP levels were similar in DISH and NDISH subjects, which is in line with a recent study on 49 men that underwent surgery for ossification of the posterior longitudinal ligament in cervical spine (OPLL). The authors observed that PINP levels were not significantly different in subjects with OPLL associated with DISH, compared to those with cervical spondylosis [41].

Regarding to bone resorption markers, we have observed no differences in serum CTX levels in subjects with or without DISH. In this sense, serum levels of tartrate-resistant acid phosphatase 5b (TRAP-5b), another biomarker of bone resorption, have been assessed in a recent report, but no differences between DISH and NDISH subjects were found [41]. With regard to the physiologic regulators of bone turnover, DISH has been related to reduced DKK-1 levels, a protein that inhibits osteogenesis induced by the Wnt/β-catenin pathway [18,19].

This pattern of high values of markers of bone formation -ALP, osteocalcin- as well as a decrease in DKK-1 levels would be consistent with the anabolic phenotype of DISH [19]. Although the idea of defining DISH as a bone-forming disorder is intuitively attractive, our study has shown that men with DISH had a higher level of ALP but also a lower TBS. These results might support the bone production/

loss *continuum* ("bone-former, bone-loser") of DISH, as Kuperus et al. [42] have recently suggested.

Our study presents the limitations inherent to its transversal design, which allows investigating for association but not for directionality or causality. Another weakness is the lack of availability of serum osteocalcin levels. Nevertheless, its main strength is that it provides an analysis of the TBS values in DISH on a wide and well-characterized prospective cohort of men over 50 years, not previously performed, to our knowledge.

Conclusion

In conclusion, TBS values were significantly lower in men diagnosed with DISH irrespective of age, BMI, and BMD. Our results might suggest that in men >50 years, the process of ligamentous ossification characteristic of DISH might be related to a worse trabecular microstructure. Besides, serum ALP levels were higher in DISH individuals supporting the idea, together with the TBS results, that DISH could be a bone production/loss *continuum* process and not a classic bone-forming disorder. Future longitudinal studies are needed to deep insight into the usefulness of TBS for assessing the risk of fracture in these patients.

Declaration of Competing Interest

None.

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